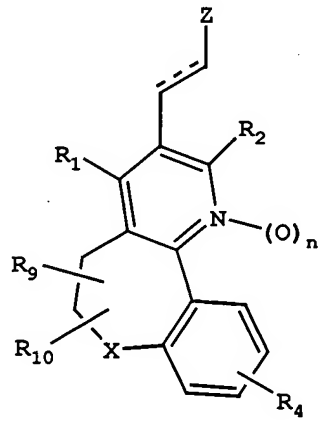
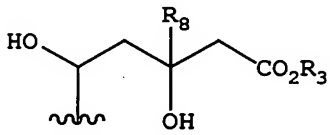
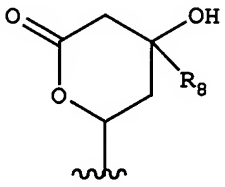
AMENDMENTS TO CLAIMS

Claims 1 to 20. (Cancelled).

Claim 21. (Currently Amended) A pharmaceutical combination comprising the HMG CoA reductase inhibitor compound having the structure



wherein X is O, S, SO, SO_2 or NR_7;

Z is  or  also referred to as the δ-lactone;

n is 0 or 1;

R_1 and R_2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R_3 is H or lower alkyl or a metal ion;

R_4 is H, halogen, CF_3, hydroxy, alkyl, alkoxy, carboxyl, carboxyalkyl-, aminoalkyl, amino, alkanoylamino, aroylamino, cyano, alkoxyCON(R_{7d})-, $R_{7f}R_{7g}NCO_2$-, $R_{7f}R_{7g}NCO$-, $R_{7e}SO_2N(R_{7d})$-, $R_{7f}R_{7g}NSO_2N(R_{7d})$-, $R_{7e}OCO_2$- or $R_{7e}OCO$;

R_7 is H, alkyl, aryl, alkanoyl, aroyl or alkoxycarbonyl, $R_{7a}SO_2$-, $R_{7b}R_{7c}NSO_2$- or $R_{7b}R_{7c}NCO$-;

R_{7a} and R_{7e} are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroaryl;

R_{7b} and R_{7c}, and R_{7f} and R_{7g}, and R_{7d} are the same or different and are independently selected from H, alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R_8 is H or lower alkyl;

R_9 and R_{10} are the same or different and are independently selected from H or alkyl; or where at least one of R_9 and R_{10} is alkyl, R_9 and R_{10} may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring, which may include a spirocyclic ring;

and ⎓ represents a single bond or a double bond (which may be cis or trans);

or a pharmaceutically acceptable salt thereof (where R_3 is H), or an ester thereof, or a stereoisomer thereof;

and another therapeutic agent which is one or more hypolipidemic agents or lipid-lowering agents, or lipid agents, or lipid modulating agents, and/or one or more other types of therapeutic agents including antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, anti-dementia agents, anti-Alzheimer's agents, anti-osteoporosis agents, and/or hormone replacement therapeutic agents, and/or other cardiovascular agents ~~(including~~ which are anti-anginal agents, anti-arrhythmic agents, anti-atherosclerosis agents, anti-inflammatory agents, anti-arthritis agents, anti-platelet agents, anti-heart failure agents[[)]], anti-cancer agents, anti-infective agents, hormone replacement agents, growth hormone secretagogues, selective androgen receptor modulators, and/or immunomodulatory agents.

Claim 22. (Currently Amended) The combination as defined in Claim 21 wherein the hypolipidemic agent or lipid-lowering agent or other lipid agent or lipid modulating agent or anti-atherosclerotic agent, which is employed comprises 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, PPAR α agonists, PPAR dual α/γ agonists, PPAR δ agonists, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, or nicotinic acid and derivatives thereof, ATP citrate lyase inhibitors, phytoestrogen compounds, ~~an~~ HDL upregulators, LDL catabolism promoters, antioxidants, PLA-2 inhibitors, antihomocysteine agents, HMG-CoA synthase inhibitors, lanosterol demethylase inhibitors, or sterol regulating element binding protein-I agents.

Claim 23. (Original) The pharmaceutical combination as defined in Claim 21 comprising said HMG CoA reductase inhibiting compound and an antidiabetic agent.

Claim 24. (Currently Amended) The combination as defined in Claim 23 wherein the antidiabetic agent which may be optionally employed is 1,2,3 or more antidiabetic agents or antihyperglycemic agents ~~including~~ which are insulin secretagogues or insulin sensitizers, which ~~may include~~ are biguanides, sulfonyl ureas, PTP-1B inhibitors, aldose reductase inhibitors, glucosidase inhibitors, PPAR γ agonists, PPAR α agonists, PPAR δ antagonists or agonists, aP2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, insulin, and/or glucagon-like peptide-1 (GLP-1) or [[a]] mimetics thereof.

Claim 25. (Original) The combination as defined in Claim 24 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A.

Claim 26. (Original) The combination as defined in Claim 21 wherein the HMG CoA reductase inhibiting compound is present in a weight ratio to the lipid-lowering agent or antidiabetic agent within the range from about 0.001:1 to about 100:1.

Claim 27. (Original) The combination as defined in Claim 21 wherein the other type of therapeutic agent which may be optionally employed is 1, 2, 3 or more of an anti-obesity agent which is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, an aP2 inhibitor, a thyroid receptor beta drug, an anorectic agent, a PTP-1B inhibitor, a CCKA agonist, a neuropeptide Y antagonist, a melanocortin-4-receptor agonist, a PPAR modulator which is a PPAR γ antagonist, PPAR α agonist, and/or PPAR δ antagonist, a leptin inhibitor such as a leptin receptor activator, a fatty acid oxidation upregulator or inducer.

Claim 28. (original) The combination as defined in Claim 27 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine,

dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol, P57 or CP-644673 (Pfizer).

Claim 29. (Original) The combination as defined in Claim 21 wherein the lipid modulating agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor and the other lipid agent is a cholesteryl ester transfer protein inhibitor.

Claim 30. (Original) The combination as defined in Claim 29 wherein the lipid modulating agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, pitavastatin, rosuvastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin, and/or LY295427.

Claim 31. (Currently Amended) The combination as defined in Claim 21 wherein the antihypertensive agent employed is an ACE inhibitor, angiotensin II receptor antagonist, NEP inhibitor, a NEP/ACE inhibitor, a calcium channel blocker, a T-channel calcium antagonist, a β-adrenergic blocker, a diuretic, [[a]] an α-adrenergic blocker, a dual action receptor antagonist (DARA), or a heart failure drug.

Claim 32. (Original) The combination as defined in Claim 31 wherein the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril;

an NEP/ACE inhibitor which is omapatrilat, gemopatrilat, or CGS 30440;

an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, or clonidine HCl, carvediol, atenolol, hydrochlorothiazide, torasemide, furosemide, spironolactone or indapamide.

Claim 33. (Original) The combination as defined in Claim 21 wherein the HMG CoA reductase inhibitor is in combination with an ACE inhibitor or a NEP/ACE inhibitor.

Claim 34. (Original) The combination as defined in Claim 21 wherein the HMG CoA reductase inhibitor is in combination with an ACE inhibitor which is rampipril.

Claim 35. (Original) The combination as defined in Claim 21 wherein the HMG CoA reductase inhibitor is in combination with a NEP/ACE inhibitor which is omapatrilat or gemopatrilat.

Claim 36. (Original) The combination as defined in Claim 21 wherein the HMG CoA reductase inhibitor is in combination with a platelet aggregation inhibitor.

Claim 37. (Original) The combination as defined in Claim 36 wherein the platelet inhibitor is clopidogrel.

Claim 38. (Original) The combination as defined in Claim 36 wherein the platelet inhibitor is clopidogrel, aspirin or a combination of clopidogrel and aspirin.

Claim 39. (Original) The combination as defined in Claim 21 wherein the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole, ifetroban, abciximab, tirofiban, eptifibatide, or anagrelide.

Claim 40. (Original) The combination as defined in Claim 21 wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is tacrine HCl (Cognex®), donepezil (Aricept®), a Υ-secretase inhibtor, a β-secretase inhibitor and/or antihypertensive agent;

an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist;

a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM);

a tyrosine kinase inhibitor;

a selective androgen receptor modulator;

an antiarrhythmic agent, which is a β-blocker, or a calcium channel blocker, or an α-adrenergic blocker;

coenzyme Q sub. 10;

an agent that upregulates type III endothelial cell nitric acid syntase;

a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (PPS), doxycycline or minocycline;

a cyclooxygenase (COX)-2 inhibitor, which is Celebrex® (Searle) or Vioxx® (Merck) or a glycoprotein IIa/IIIb receptor antagonist;

a 5-HT reuptake inhibitor;

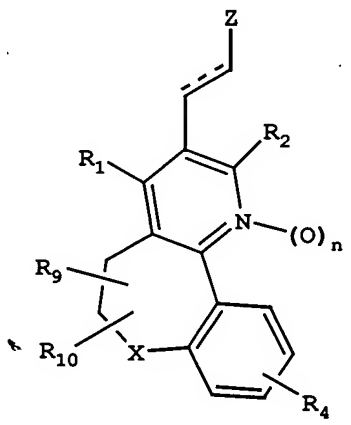
a growth hormone secretagogue;

an anti-atherosclerosis agent;

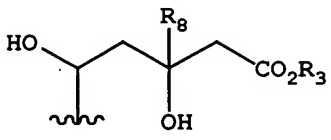
an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

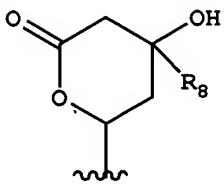
Claims 41 to 45. (Cancelled).

Claim 46. (Currently Amended) A method for treating cholesterol related diseases, diabetes and related diseases, cardiovascular diseases, cerebrovascular diseases, or for improving coagulation homeostasis, reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a combination of a compound having the structure



wherein X is O, S, SO, SO_2 or NR_7;

Z is 

or 

(also referred to as the δ-lactone);

n is 0 or 1;

R_1 and R_2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R_3 is H or lower alkyl or a metal ion;

R_4 is H, halogen, CF_3, hydroxy, alkyl, alkoxy, carboxyl, carboxyalkyl-, aminoalkyl, amino, alkanoylamino, aroylamino, cyano, alkoxyCON(R_{7d})-, $R_{7f}R_{7g}NCO_2$-, $R_{7f}R_{7g}NCO$-, $R_{7e}SO_2N(R_{7d})$-, $R_{7f}R_{7g}NSO_2N(R_{7d})$-, $R_{7e}OCO_2$- or $R_{7e}OCO$;

R_7 is H, alkyl, aryl, alkanoyl, aroyl or alkoxycarbonyl, $R_{7a}SO_2$-, $R_{7b}R_{7c}NSO_2$- or $R_{7b}R_{7c}NCO$-;

R_{7a} and R_{7e} are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroaryl;

R_{7b} and R_{7c}, and R_{7f} and R_{7g}, and R_{7d} are the same or different and are independently selected from H, alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

or R_{7b} and R_{7c} may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring, which, where applicable, includes 1 to 3 heteroatoms in the ring; or R_{7f} and R_{7g} may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered ring, which, where ~~appicable~~ applicable, includes 1 to 3 heteroatoms in the ring.

R_8 is H or lower alkyl;

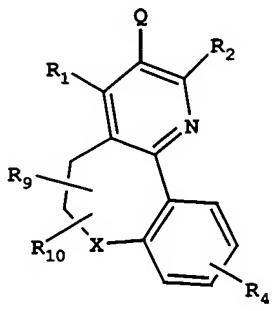
R_9 and R_{10} are the same or different and are independently selected from H or alkyl; or where at least one of R_9 and R_{10} is alkyl, R_9 and R_{10} may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring, which may include a spirocyclic ring;

and  represents a single bond or a double bond (which may be cis or trans);

or a pharmaceutically acceptable salt thereof (where R_3 is H), or an ester thereof, or a stereoisomer thereof;

and another therapeutic agent which is a hypolipidemic agent, and/or lipid modulating agent and/or antidiabetic agent and/or cardiovascular agent, cerebrovascular agent, and/or other type of therapeutic agent~~, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of such combination~~.

47. (Original) A compound having the structure



wherein X is O, S, SO, SO_2 or NR_7 where R_7 is H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, $R_{7a}SO_2$-, $R_{7b}R_{7c}NSO_2$-or $R_{7b}R_{7c}NCO$;

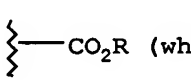
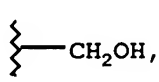
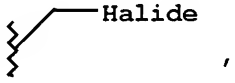
R_1 and R_2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

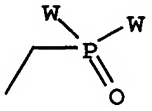
R_4 is H, halogen, CF_3, hydroxy, alkyl, alkoxy, alkanoylamino, aroylamino, cyano, alkoxyCON(R_{7d})-, $R_{7f}R_{7g}NCOalkoxy$-, $R_{7e}SO_2N(R_{7d})$- or $R_{7f}R_{7g}NSO_2N(R_{7d})$-;

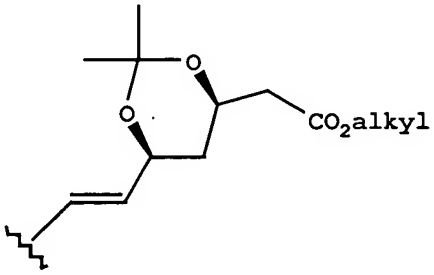
R_{7a} and R_{7e} are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R_{7b} and R_{7c}, and R_{7f} and R_{7g}, and R_{7d} are the same or different and are independently selected from H, alkyl, arylalkyl, cycloalkyl, alkenyl, aryl, heteroaryl or cycloheteroalkyl;

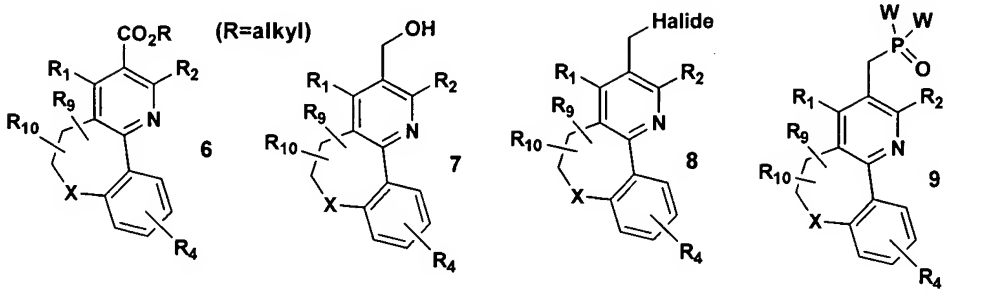
R_9 and R_{10} are the same or different and are independently selected from H or alkyl, or R_9 and R_{10} may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring;

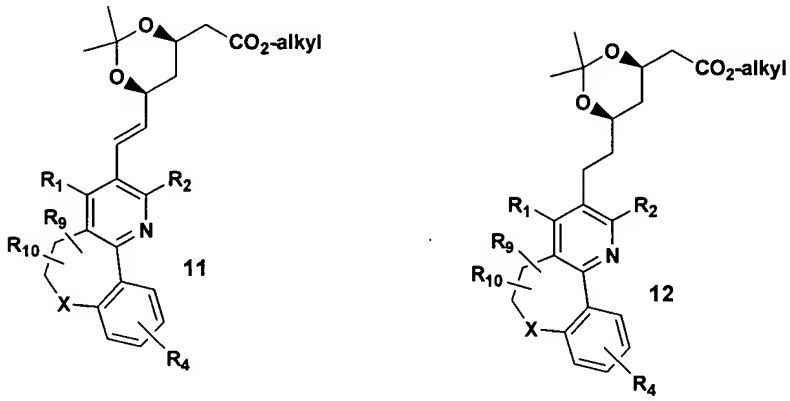
Q is  (CO_2R (where R is alkyl),  (CH_2OH, 

 (where W is aryl, alkyl, or alkoxy),

or 

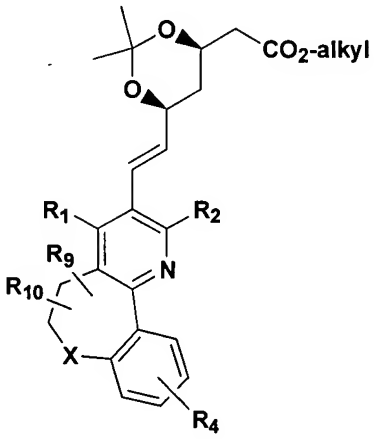
Claim 48. (Original) The compound as defined in Claim 47 having the following structures:





Claim 49. (Cancelled).

Claim 50. (New) A process for preparing an intermediate of the structure 11



wherein

X is O, S, SO, SO_2 or NR_7;

R_1 and R_2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R_4 is H, halogen, CF_3, hydroxy, alkyl, alkoxy, carboxyl, carboxylalkyl-, aminoalkyl, amino, alkanoylamino, aroylamino, cyano, alkoxyCON(R_{7d})-, $R_{7f}R_{7g}NCO$-, $R_{7f}R_{7g}NCO_2$-, $R_{7e}SO_2N(R_{7d})$-, $R_{7f}R_{7g}NSO_2N(R_{7d})$-, $R_{7e}OCO_2$- or $R_{7e}OCO$-;

R_7 is H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, $R_{7a}SO_2$-, $R_{7b}R_{7c}NSO_2$- or $R_{7b}R_{7c}NCO$-;

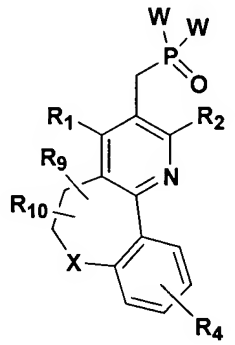
R_{7a} and R_{7e} are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl,

R_{7b} and R_{7c}, and R_{7f} and R_{7g}, and R_{7d} are the same or different and are independently selected from H, alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; or R_{7b} and R_{7c} may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring, which where applicable, includes a total of 1 to 3 heteroatoms in the ring, which heteroatoms may be N, O or S; or R_{7f} and R_{7g} may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring which, where applicable, includes a total of 1 to 3 heteroatoms in the ring, which heteroatoms may be N, O or S;

R_9 and R_{10} are the same or different and are independently selected from H or alkyl, or where at least one of R_9 and R_{10} is alkyl, R_9 and R_{10} may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring, which may include a spirocyclic ring;

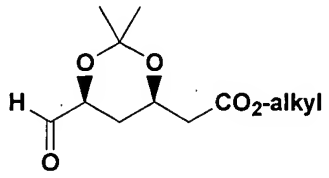
which comprises

providing a phosphorus compound of the structure



where W is aryl or alkoxy

and reacting the phosphorus compound with an aldehyde of the structure



under Witting conditions in the presence of a base to form intermediate 11.

Claim 51. (New) The process as defined in Claim 50 wherein the reaction is carried out at -78°C.

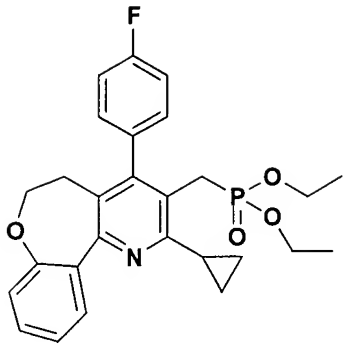
Claim 52. (New) The process as defined in Claim 50 wherein the base is n-butyl lithium, $LiN(TMS)_2$ or LDA.

Claim 53. (New) The process as defined in Claim 50 wherein the reaction is carried out in the presence of a solvent which is THF, Et_2O, toluene or DMPU.

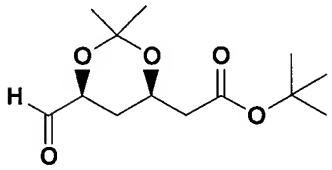
Claim 54. (New) The process as defined in Claim 50 wherein the reaction is carried out at a temperature of -78°C., the base is n-butyl lithium, $LiN(TMS)_2$ or LDA, in the presence of a solvent which is THF, Et_2O, toluene or DMPU.

Claim 55. (New) The process as defined in Claim 54 wherein the base is n-butyl lithium, and the solvent is THF.

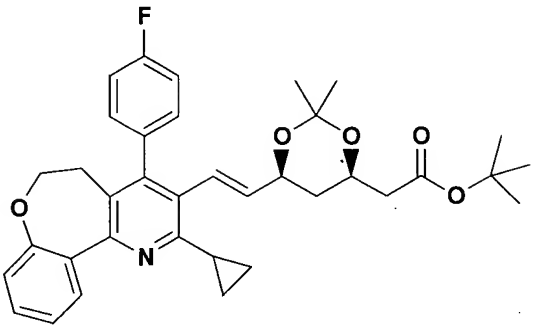
Claim 56. (New) The process as defined in Claim 50 wherein the phosphorus compound has the structure



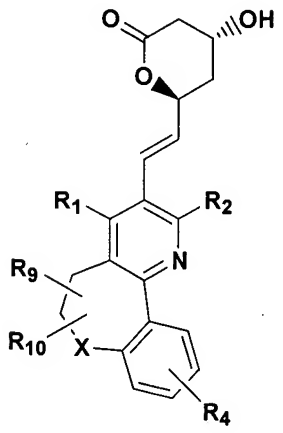
the aldehyde has the structure



and the intermediate 11 has the structure



Claim 57. (New) A process for preparing a lactone of the structure 1a



wherein

X is O, S, SO, SO_2 or NR_7;

R_1 and R_2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R_4 is H, halogen, CF_3, hydroxy, alkyl, alkoxy, carboxyl, carboxylalkyl-, aminoalkyl, amino, alkanoylamino, aroylamino, cyano, alkoxyCON(R_{7d})-, $R_{7f}R_{7g}NCO$-, $R_{7f}R_{7g}NCO_2$-, $R_{7e}SO_2N(R_{7d})$-, $R_{7f}R_{7g}NSO_2N(R_{7d})$-, $R_{7e}OCO_2$- or $R_{7e}OCO$-;

R_7 is H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, $R_{7a}SO_2$-, $R_{7b}R_{7c}NSO_2$- or $R_{7b}R_{7c}NCO$-;

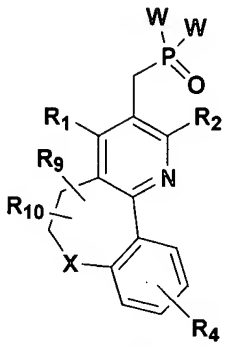
R_{7a} and R_{7e} are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl,

R_{7b} and R_{7c}, and R_{7f} and R_{7g}, and R_{7d} are the same or different and are independently selected from H, alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; or R_{7b} and R_{7c} may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring, which where applicable, includes a total of 1 to 3 heteroatoms in the ring, which heteroatoms may be N, O or S; or R_{7f} and R_{7g} may be taken together with the nitrogen to which they are attached to form a stable 3 to 8 membered heterocyclic ring which, where applicable, includes a total of 1 to 3 heteroatoms in the ring, which heteroatoms may be N, O or S;

R_9 and R_{10} are the same or different and are independently selected from H or alkyl, or where at least one of R_9 and R_{10} is alkyl, R_9 and R_{10} may be taken together with the carbon or carbons to which they are attached to form a 3 to 7 membered carbocyclic ring, which may include a spirocyclic ring;

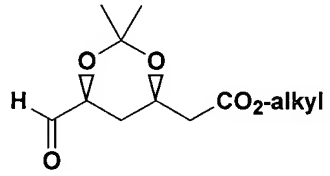
which comprises

providing a phosphorus compound of the structure

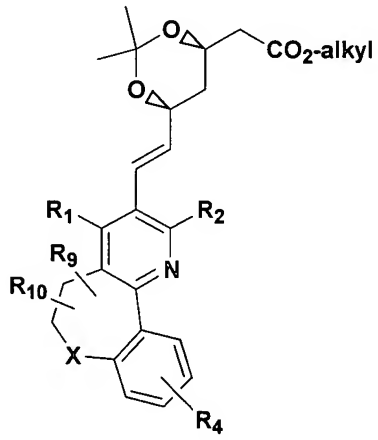


where W is aryl or alkoxy

reacting the phosphorus compound with an aldehyde of the structure

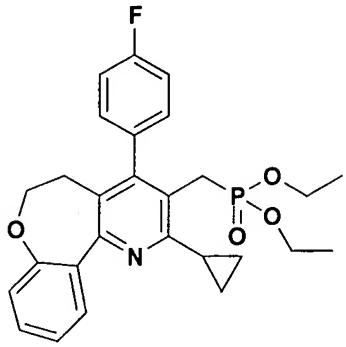


in the presence of a base at a temperature of -78°C to form intermediate 11

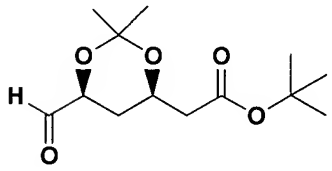


and treating intermediate 11 with an acid to form the lactone Ia.

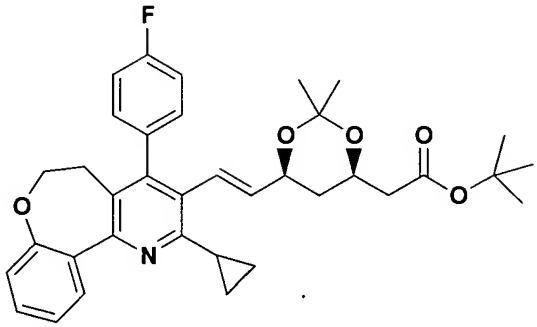
Claim 58. (New) The process as defined in Claim 57 wherein the phosphorus compound has the structure



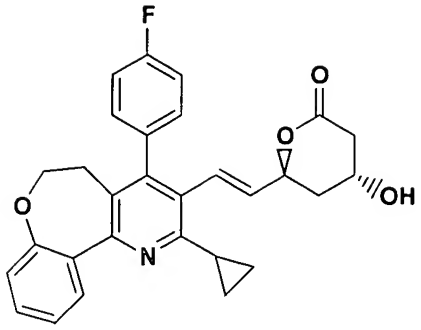
the aldehyde has the structure



the intermediate 11 has the structure



and the lactone has the structure



Claim 59. (New) The process as defined in Claim 57 wherein the acid is trifluoroacetic acid or hydrochloric acid.

Claim 60. (New) The process as defined in Claim 57 wherein the reaction of the phosphorus compound and aldehyde is carried out at a temperature of -78°C, the base is n-butyl lithium, in the presence of THF as a solvent.